UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/717,597	11/21/2003	Natalie C. Twine	WYE-021	3640

54623 7590 10/23/2006

KIRKPATRICK & LOCKHART NICHOLSON GRAHAM LLP/WYETH
STATE STREET FINANCIAL CENTER
ONE LINCOLN STREET
BOSTON, MA 02111-2950

EXAMINER	
LIU, SUE XU	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 10/23/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	Application No. 10/717,597	Applicant(s) TWINE ET AL.	
	Examiner Sue Liu	Art Unit 1639	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 14 September 2006 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires *3* months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1-10,12,13 and 15-17*.
   Claim(s) withdrawn from consideration: *14*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☒ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

MARK SHIBUYA, PH.D.
PATENT EXAMINER

Continuation Sheet

Continuation of item 11:

The following rejections are maintained for the reason of record:

1.) Claims 1, 2, 4-7, 9-13 and 16-18 are rejected under 35 U.S.C. 103(a) as being obvious over Ralph et al (US 6,190,857 B1; 2/20/2001), in view of Liu et al (Infection and Immunity. Vol. 69: 2788-2796; 2001).

2.) Claims 1-10, 12, 13, and 15-17 are rejected under 35 U.S.C. 103(a) as being obvious over Ralph et al (US 6,190,857 B1; 2/20/2001), in view of Golub et al (Science. Vol. 286: 531-527; 1999) and Liu et al (Infection and Immunity. Vol. 69: 2788-2796; 2001).

Applicant's arguments and Declaration (by Michael E. Burczynski) have been fully considered, and they are not persuasive for the following reasons (in addition to reasons of record):

Applicant's Declaration is not sufficient to overcome the above listed rejections.

The Declaration by Dr. Michael e. Burczynski states that the "only a minority of transcripts display statistically significant differential expression," and "would not have expected most genes involved with NFkappaB signaling to be differentially expressed in peripheral blood mononuclear cells (PBMCs) of patients having a non-blood diseases such as RCC as compared to PBMCs of disease-free humans."

However, the question in the instant application is whether a person of ordinary skill in the art would be motivated to compare the expression profile of TLR2 in patients having a solid

tumor using PBMCs samples. The above statement from the Declaration is generic in term of genes that may or may not be differentially expressed in PBMCs of patients having tumors, and is not directed to the specific TLR2 gene. Furthermore, the above statements from the Declaration provide evidence to show that one of ordinary skill in the art would have been motivated to compare TLR2 gene expression, because a certain number of genes involved in the NFkappaB signaling pathway are known and shown to be differentially expressed.

The Declaration also discusses a study using Affymetrix gene chip to analyze differential expression of genes involved in the NFkappaB signaling pathway. Applicant's study shows that a portion of the NFkappaB targeted genes are differentially expressed. Again, this provides motivation for one of ordinary skill in the art to use genes involved in NFkappaB tumor signaling pathway for differential gene expression comparison.

Furthermore, the genes studied and discussed in the Declaration are NFkappaB targeted genes as indicated by the Feuerhake reference (cited by Applicants' in the Declaration). However, TLR2 gene is involved in the activation of NFkappaB (as taught by Liu et al; cited previously), and is not a downstream signaling target of NFkappaB. The activation of NFkappaB would require TLR2 activation, and thus providing motivation to monitor TLR2 gene expression, and reasonable expectation of success.

The study discussed in the Declaration also recites that only a number of genes (4 genes) had expression "altered at least 2-fold with a statistical significance in a t-test of less than 0.05", which data is used in the Declaration to show that only a small percentage of NFkappaB targeted genes were differentially expressed. This is not found persuasive to overcome the above listed rejections. First, it is not clear what is the exact percentage of genes from the total gene set is

differentially expressed. The study discussed in the Declaration does not clearly indicate how many genes were monitored. More importantly, the instant Claim does not recite limitation that the genes used in the method have to be differentially expressed "at least 2-fold with a statistical significance in a t-test of less than 0.05". The instant claim language is broadly drawn to a method of comparing one or more gene expression in different samples (e.g. patients with and without tumors). Thus, the specific statistical criterion used in the study is irrelevant to the discussion of the outstanding rejections over the instant claimed invention.

A person of ordinary skill in the art would have been motivated to compare gene expression of genes that are known to be involved in the tumor signaling pathways. As discussed above, TLR2 gene is known to be involved in the tumor pathway, and expressed in PBMCs (as taught by Liu et al), a person of ordinary skill in the art would have been motivated at the time the invention was made to compare TLR2 gene expression between patients with and without tumors.

Applicants argue that there is no motivation to combine the Ralph and the Liu references. Specifically, Applicants argue that Liu "does not provide any teaching, suggestion, or motivation, either explicitly or implicitly, that TLR2 should be used as a gene marker for solid tumor diagnosis".

Applicants argue that there is no motivation to combine the Ralph and Liu references, because the Liu reference is directed to different gene expression in response to macrophage defense against gram-positive bacteria. Applicants' argument is not found persuasive. As pointed out by applicants, the Liu reference does teach TLR2 gene expression in macrophage in response

to bacterial invasion. However, the Liu reference also teaches that the TLR2 gene is expressed in PBMCs and involved in the signaling pathway of NF-κB of the immunosystem. Liu et al teach that TLR2 activates NF-κB (see pg 2788, right col., 1st para of the Liu reference), which is known to be involved in tumor signaling pathway, as evidenced by Mayo et al (cited previously). In addition, Ralph et al teach the immune system is an attractive choice to survey because it would be expected to respond robustly to a malignant disease process. Ralph et al also teach the examination of peripheral blood mononuclear cell population has advantage of providing evidence of cancer presence without requiring any knowledge of its physical location in the body (see para. 472 of the Ralph reference). In summary, Ralph et al teach gene expression profile (i.e. genes that are either up or down regulated in blood), and the advantage of monitoring gene expression profile using peripheral blood mononuclear cell population. Therefore, Ralph et al provide strong motivation to study gene expression profile using samples derived from peripheral blood mononuclear cells (PBMCs). Because Ralph et al teach the advantage of studying different gene expression in the immune system using sample derived from PBMCs, one of ordinary skill in the art would have been motivated to study genes that are know to be expressed in PBMCs, and are also known to be involved in the signal pathway of the immunosystem. In addition, Ralph et al teach methods of detecting cancer in subjects by measuring gene expression levels of genetic markers (see Abstract of the Ralph reference). Therefore, a person of ordinary skill in the art would have been motivated to use TLR2 as a genetic marker for cancer due to the involvement of TLR2 in the tumor signaling pathway (as taught by Liu), and to monitor TLR2 gene expression profile using samples derived from PBMCs to monitor cancer progression and/or diagnosis.

Thus, both the Ralph and the Liu references provide strong motivations to combine the references, and to compare TLR2 gene expression in samples derived from subjects with and without tumors.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Applicants also argue that there is no reasonable expectation of success that TLR2 could be used as a gene marker for solid tumor diagnosis.

In response to applicant's argument, Ralph et al have demonstrated the success of a method of comparing gene expression profiles in patients and non-patients using samples derived from PBMCs. Liu et al teach that TLR2 gene is known and differentially expressed in PBMCs. In addition, the techniques for monitoring gene expression profiles for various genes are known in the art as demonstrated by Ralph et al and Liu et al. One of ordinary skill in the art would have reasonable expectation of success to compare gene expression profiles of specific genes (such as TLR2) that are known in the art using known methods and techniques.

Applicants' argument regarding the claim rejection over the combination of the Ralph, Golub and Liu references are similar to the arguments stated above.

Applicants are respectively directed to the above discussion for answer to the arguments.